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ORIGINAL ARTICLE

Ibandronate for the prevention of bone loss after allogeneic stem cell transplantation for hematologic malignancies: a randomized-controlled trial

Huifang Lu[1], Richard E Champlin[2], Uday Popat[2], Xerxes Pundole[1], Carmelita P Escalante[1], Xuemei Wang[3], Wei Qiao[3], William A Murphy[4] and Robert F Gagel[5]

[1]Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [2]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [4]Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [5]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

The purpose of this study was to evaluate the effects of ibandronate on bone loss following allogeneic stem cell transplantation (allo-SCT). A single-centered, open-label prospective randomized-controlled study following allo-SCT. The treatment group received 3 mg of intravenous ibandronate quarterly starting within 45 days of allo-SCT. All patients received daily calcium and vitamin D supplements. We compared the changes in bone mineral density (BMD) in the lumbar spine, femoral neck and total hip at 6 and 12 months following allo-SCT between the control and treatment groups. We also assessed relationships between bone loss and cumulative glucocorticoid dose, cumulative tacrolimus dose and acute and chronic graft-versus-host disease (GVHD) by linear regression. In all, 78 patients were enrolled. The treatment group had significantly less BMD loss in the lumbar spine at 6 months (mean percent change 0.06 ± 4.03 (treatment group) versus -2.61 ± 4.2 (control group)) and 12 months (mean percent change 1.27 ± 5.29 (treatment group) versus -1.81 ± 4.49 (control group)) than the control group ($P = 0.03$). Both groups lost more BMD in the femoral neck and total hip than in the lumbar spine at 6 and 12 months. The changes in BMD in the femoral neck and total hip did not differ significantly between groups. Both glucocorticoids and tacrolimus reduced BMD in the lumbar spine, but ibandronate prevented this loss. Ibandronate may reduce bone loss in the lumbar spine in patients who undergo allo-SCT, particularly those who have received high doses of glucocorticoids and/or tacrolimus.

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Introduction

Long-term stem cell transplantation survivors commonly develop bone loss with a subsequent increase in fracture risk.[1] This is especially true for allogeneic stem cell transplantation (allo-SCT) where 50% of patients suffer bone loss.[2–4] Bone loss occurs rapidly during the first 3–6 months after the transplant,[5] and most commonly in the lumbar spine and femoral neck.[6] Importantly the bone loss is not recovered in long-term survivors.[7]

Bone loss following allo-SCT has a complex pathogenesis involving both reduced bone formation and increased bone resorption. A key contributor to this is that 50% of allo-SCT recipients develop some form of graft-versus-host disease (GVHD) which necessitates prolonged use of glucocorticoids and immunosuppressive agents such as tacrolimus that have been implicated in post-transplant bone loss.[5,8] Other factors such as older age, prolonged inactivity and genetic predisposition may also contribute to post-transplant bone loss.[8,9]

Correspondence: Dr H Lu, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail: hlu@mdanderson.org

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Treatment with bisphosphonates beginning immediately after allo-SCT may prevent the accelerated bone resorption that develops and could mitigate bone loss. Antiresorptive therapy increases bone mineral density (BMD) and reduces fractures in other populations, including patients who have undergone solid organ transplant.[10–13] A few randomized-controlled studies have been conducted to assess the effects of bisphosphonates in preventing or treating bone loss following allo-SCT. A randomized study of risedronate in patients following allo-SCT showed that it increased BMD in the lumbar spine and prevented bone loss in the femoral neck.[14] Another randomized study of zoledronic acid in hypogonadal young women following allo-SCT showed an increase in both lumbar and femoral neck BMD.[15] Similar results were observed in another study of zoledronic acid.[16] Two studies of pamidronate in allo-SCT patients showed some promise. In one study, treatment with pamidronate decreased bone loss of the lumbar spine and femoral neck; however, bone loss was not completely prevented in the hip.[17] In another study, treatment with pamidronate initiated before allo-SCT decreased bone loss significantly in the lumbar spine, total hip and femoral neck.[18] Although the results of these randomized trials are promising, none of the oral bisphosphonates tested abolished bone loss in the hip and femoral neck completely. In three studies the intravenous (i.v.) form of zoledronic acid at a dose of 4 mg i.v. before allo-SCT, and at 3 and 6 months after[16] a dose of 4 mg i.v. every 28 days for 3 months[19] and at a dose of 4 mg i.v. at 2 months after allo-SCT and then every 3 months until 2 years[20] (in doses higher than the usual dose in treating osteoporosis), prevented bone loss at the femoral neck.[16,19,20] Collectively, these studies suggest the need for a different bisphosphonate or dosing regimens for more durable maintenance of bone mass following transplantation.

Ibandronate, in oral or i.v. form, has been shown to significantly increase BMD in the spine and hip, and decrease the incidence of vertebral fractures in post-menopausal women.[21–23] There have been some controversies about the effects of ibandronate on non-vertebral fractures in the literature. A *post hoc* analysis conducted by Rossini *et al.*[24] by combining various doses of oral and i.v. ibandronate from several studies, none of which were designed to evaluate the risk of non-vertebral fracture, concluded that ibandronate has sustained vertebral an non-vertebral anti fracture efficacy.[24]

To our knowledge, ibandronate has not been studied for the prevention of bone loss after allo-SCT in a randomized fashion. We conducted a prospective randomized placebo-controlled trial to study the effects of treatment with ibandronate on BMD changes following allo-SCT.

Results

Patients

We screened 414 patients for the trial and ultimately enrolled 78. Although we had intended to enroll more, financial and time constraints limited enrollment. The predominant reason that patients left the study after enrollment in both the control and treatment groups was disease relapse (**Figure 1**). None of the baseline characteristics differed significantly between the two randomized groups. At baseline most patients had normal lumbar spine, femoral neck and total hip BMD measurements (**Table 1**). Most patients had normal calcium, intact parathyroid hormone and creatinine levels at baseline (Supplementary Table 1); however, 50 patients (64%) were deficient in vitamin D ($<20\,ng\,ml^{-1}$) at baseline.

Primary outcome (BMD)

Changes in BMD in the control and treatment groups at 6 and 12 months relative to baseline are shown in **Table 2**. In the control group, significant BMD loss occurred in the lumbar spine at 6 months, but in the treatment group, no significant BMD loss in the lumbar spine was seen at 6 and 12 months. The mean percentage change in BMD in the lumbar spine differed significantly between the two groups at both 6 and 12 months (**Table 2**; **Figure 2a**).

In both the treatment and the control groups, significant BMD loss occurred in the femoral neck (**Figure 2b**) and total hip (**Figure 2c**) at 6 and 12 months relative to baseline. However, the percentage changes in BMD in the total hip and in the femoral neck at 6 and 12 months did not differ significantly between the two groups (**Table 2**).

Secondary outcomes

No bone fractures occurred in either group during the study. Ibandronate was well-tolerated; adverse effects reported were those common after allo-SCT. The most common symptom reported in both groups was bone and joint pain. Compliance measured by number of pills taken was similar between the two groups at both 6 and 12 months. All patients' transplanted with stem cells had engrafted at 1 month.

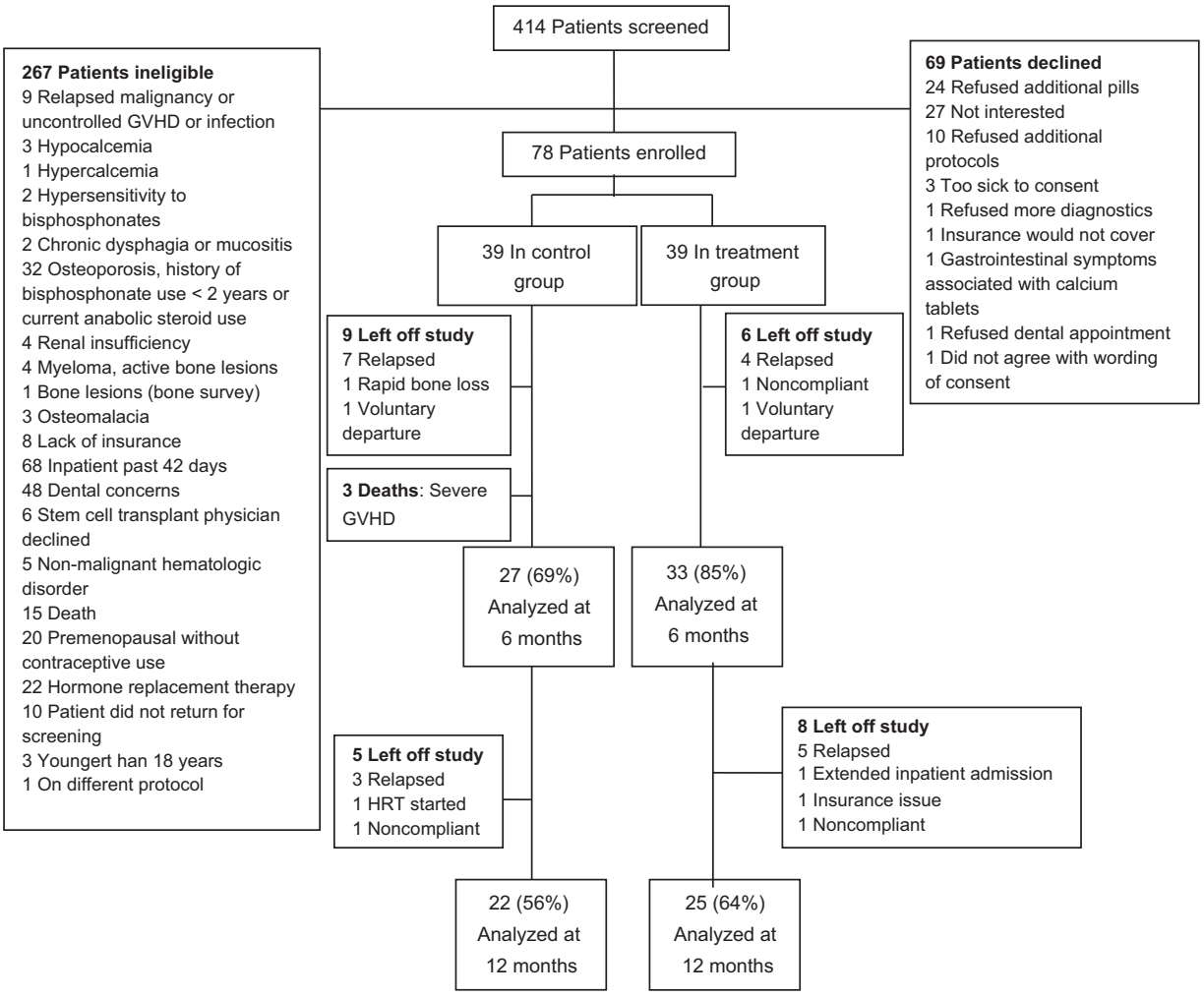
Multivariable analysis

We tested the association between use of tacrolimus and glucocorticoids and the percentage changes in lumbar spine BMD at 6 and 12 months. At 12 months each unit increase in the tacrolimus dose was associated with a 0.003% decrease in lumbar spine BMD relative to baseline after adjusting for the cumulative glucocorticoid dose and ibandronate use. Ibandronate had a significant protective effect on the BMD of the lumbar spine at both 6 and 12 months (**Table 3**).

In the multivariable analysis, none of the variables showed a significant effect on the percentage change in BMD of the femoral neck at 6 months relative to baseline. At 12 months acute GVHD was associated with a 3.73% decrease in femoral neck BMD relative to baseline after adjusting for the effects of cumulative tacrolimus dose and ibandronate use (**Table 3**). Similarly, normal baseline BMD was associated with a 2.19% change in total hip BMD relative to baseline after adjusting for the effect of acute GVHD, glucocorticoid use and ibandronate use at 6 months. None of the variables showed a significant effect on percentage change in BMD of the total hip at 12 months (**Table 3**).

Discussion

We found that patients treated with i.v. ibandronate after allo-SCT had significantly less BMD loss in the lumbar spine at 6 and 12 months compared with controls, suggesting that ibandronate prevented lumbar spine bone loss. In fact, in patients receiving ibandronate, the mean BMD in the lumbar spine was slightly higher at 6 and 12 months than at baseline. In the femoral neck and total hip the decline in BMD was attenuated by ibandronate therapy, although not significantly so, implying that



GVHD, graft-versus-host disease; HRT, hormone replacement therapy.

Figure 1 Trial enrollment summary. GVHD, graft-versus-host disease; HRT, hormone replacement therapy.

treatment with ibandronate is no more effective than supplementation with calcium and vitamin D at preventing bone loss in these areas following allo-SCT. One possible explanation for this outcome is that ibandronate may not be sufficient in inhibiting resorption in cortical bone, a major component of the hip, than in trabecular bone. Another explanation could be that our study did not have sufficient power to detect a difference as the accrual goals were not met due to early termination of the study as a result of financial constraints.

Our results support those of other studies that indicate bisphosphonates may reduce bone loss after allo-SCT. In a study by Grigg *et al.*,[18] pamidronate was found to completely prevent bone loss in the lumbar spine and to prevent some bone loss in the femoral neck and total hip at 3, 6, 12 and 24 months after allo-SCT. As in our study, maximum bone loss occurred at the femoral neck and total hip; however, the protective effect of pamidronate against bone loss at those sites was significant only in patients who received moderate-to-high doses of glucocorticoids and immunosuppressants. The differences in BMD of the femoral neck and total hip between our study and the study by Grigg *et al.*[18] may be attributable in part to the smaller number of patients, higher median age, predominance of male patients and smaller proportion of patients receiving stem cells from related donors in our study.

In the study by Hari *et al.*,[16] three doses of zoledronic acid at 3-month intervals were administered before SCT to those with osteopenia on pre-SCT DEXA scan and considered to be at high risk of post transplantation bone loss. Zoledronic acid prevented bone loss at the lumbar spine and femoral neck.[16] This total dose is higher than the US Food and Drug Administration-approved recommended dose for the prevention or treatment of osteoporosis in post-menopausal women (5 mg every year or every 2 years). This study assessed outcomes in those considered at high risk for post-transplant bone loss and the high dose of zoledronic acid may account for the differences in preventing femoral neck bone loss compared with ours.

Our results are similar to a 4 arm study by Tauchmanova *et al.*,[15] in which compared with those not receiving bisphosphonates, risedronate increased lumbar spine BMD and not femoral BMD. In the same study zoledronic acid increased lumbar spine and femoral neck BMD. The optimal duration and frequency of bisphosphonate therapy for the

Table 1 Baseline patient characteristics ($n = 78$)

Characteristic	*No. of patients (%)*[a]		P-*value*[b]
	Control group	*Treatment group*	
Total	39	39	
Age at transplant, years			0.24
Mean ± s.d. (median)	50.2 ± 12.9 (53)	53.3 ± 11.6 (55)	
Range	20–70	20–68	
Sex			1.00
Male	28 (72)	27 (69)	
Female	11 (28)	12 (31)	
Ethnicity			0.69
African-American	0 (0)	1 (3)	
Asian	0 (0)	1 (3)	
Hispanic	10 (26)	8 (21)	
White	29 (74)	28 (72)	
Other	0 (0)	1 (3)	
Disease			
ALL	4 (10)	3 (8)	
AML	11 (28)	16 (41)	
CLL	6 (15)	3 (8)	
CML	4 (10)	1 (3)	
Hodgkin lymphoma	1 (3)	1 (3)	
MDS	3 (8)	4 (10)	
Myelofibrosis	3 (8)	1 (3)	
NHL	7 (18)	10 (26)	
Donor type			1.00
Related	20 (51)	19 (49)	
Unrelated	19 (49)	20 (51)	
Stem cell origin			0.57
Bone marrow	2 (5)	5 (13)	
Peripheral blood	34 (87)	31 (79)	
Cord blood	2 (5)	3 (8)	
Bone marrow and peripheral blood	1 (3)	0 (0)	
No. stem cells infused, mean ± s.d. *(median)*			
TNC, $10^8\,kg^{-1}$	9.2 ± 5.0 (8.9)	8.1 ± 4.9 (7.4)	0.23
$CD34^+$, $10^6\,kg^{-1}$	5.2 ± 2.8 (5.2)	6.6 ± 6.5 (5.2)	0.74
$CD3^+$, $10^8\,kg^{-1}$	2.0 ± 1.2 (2.0)	1.7 ± 1.2 (1.6)	0.34
Conditioning regimen			0.64
Myeloablative	25 (64)	22 (56)	
Non-myeloablative	14 (36)	17 (44)	
Baseline hormonal status (women)			
Pre-menopausal	0 (0)	1 (8)	
Post-menopausal	11 (100)	11 (92)	
Men[c]			
Normal	16 (70)	15 (60)	
Hypogonadal	7 (30)	10 (40)	
GVHD prophylaxis			0.15
Tacrolimus only	0 (0)	5 (13)	
Tacrolimus and corticosteroid	2 (5)	2 (5)	
Tacrolimus and methotrexate	24 (62)	20 (51)	
Tacrolimus, corticosteroid, and methotrexate	13 (33)	12 (31)	
Bone mineral density, mean ± s.d. *(median),* $g\,cm^{-2}$			
Lumbar spine	1.07 ± 0.13 (1.06)	1.05 ± 0.15 (1.02)	0.31
Total hip	0.97 ± 0.13 (0.98)	0.98 ± 0.13 (0.98)	0.72
Femoral neck	0.84 ± 0.09 (0.85)	0.83 ± 0.11 (0.81)	0.56

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; TNC, total nucleated cells.
[a]Percentages may not add up to 100 owing to rounding.
[b]*P*-values calculated by Wilcoxon's rank-sum test for continuous variables and Fisher's exact test for categorical variables.
[c]Only 48 of the 55 male patients had baseline hormonal status checked.

treatment of allo-SCT–related osteoporosis are unclear. About half of the administered bisphosphonate dose rapidly binds to active sites of bone resorption on osteoclastic surfaces, and the remainder of the dose is excreted through the kidneys. The amount of bisphosphonate retained varies between patients and across conditions, and reflects the complex variation in the associated bone turnover.[25]

In general, i.v. ibandronate was well-tolerated by patients in our study. No bone fractures were reported in either group. Our study had several limitations. Because we analyzed data at

Table 2 Percentage changes in bone mineral density from baseline to 6 months and baseline to 12 months

Location	*Control group*				*Treatment group*				
	n	*Mean change (s.d.), %*	*Median change (range), %*	P-*value* versus *baseline*[a]	n	*Mean change (s.d.), %*	*Median change (range), %*	P-*value* versus *baseline*[a]	P-*value, treatment* versus *control*[a]
Baseline to 6 months									
Lumbar spine	27	−2.61 (4.2)	−2.2 (−14.22, 2.59)	**0.004**	33	0.06 (4.03)	−0.53 (−6.94, 11.06)	0.901	**0.03**
Femoral neck	27	−4.85 (5.37)	−5 (−16.56, 5.48)	<**0.001**	32	−3.63 (4.18)	−4.82 (−10.80, 4.60)	<**0.001**	0.33
Total hip	27	−4.72 (4.32)	−3.87 (−14.00, 2.32)	<**0.001**	32	−2.73 (3.88)	−2.74 (−13.06, 6.57)	<**0.001**	0.10
Baseline to 12 months									
Lumbar spine	23	−1.81 (4.49)	−0.79 (−10.44, 4.32)	0.089	24	1.27 (5.29)	2.34 (−14.46, 10.76)	0.137	**0.02**
Femoral neck	23	−5.20 (5.25)	−6.36 (−17.72, 7.19)	**0.001**	23	−4.29 (5.71)	−4.15 (−14.17, 9.14)	**0.002**	0.81
Total hip	23	−5.68 (5.15)	−4.95 (−15.89, 4.08)	<**0.001**	23	−4.85 (5.47)	−−3.45 (−17.77, 4.30)	<**0.001**	0.44

[a]*P*-values in bold are statistically significant.

Table 3 Multivariable analysis of factors potentially affecting BMD at 6 and 12 months

Variable	*Lumbar spine parameter: mean percentage change in BMD (*P-*value*[a]*)*		*Femoral neck parameter: mean percentage change in BMD (*P-*value*[a]*)*		*Total hip parameter: mean percentage change in BMD (*P-*value*[a]*)*	
	6 months	*12 months*	*6 months*	*12 months*	*6 months*	*12 months*
Baseline BMD (normal versus osteopenic)	NA	NA	2.38 (0.06)	NA	2.19 **(0.04)**	NA
Myeloablation (yes versus no)	NA	NA	−2.02 (0.1)	NA	NA	NA
Acute GVHD (yes versus no)	NA	NA	−2.29 (0.07)	−3.73 **(0.02)**	−1.95 (0.12)	−2.48 (0.11)
Tacrolimus	−0.002 (0.31)	−0.003 **(0.03)**	NA	−0.002 (0.2)	NA	−0.003 (0.06)
Glucocorticoids	−0.0003 (0.28)	−0.0003 (0.31)	NA	NA	−0.0003 (0.27)	NA
Group (treatment versus control)	2.43 **(0.03)**	2.81 **(0.04)**	0.88 (0.47)	1.03 (0.51)	1.65 (0.11)	0.63 (0.68)

Abbreviations: BMD, bone mineral density; GVHD, graft-versus-host disease; NA, not analyzed.
Chronic GVHD was not used in the multivariable model because $P > 0.2$ in the univariable model.
[a]*P*-values in bold are statistically significant.

multiple time points (6 and 12 months), we cannot rule out the possibility of an inflated type I error in our study. The relatively short follow-up period limits our ability to make any definitive judgment on long-term bone health.

In conclusion, our results indicate that i.v. ibandronate can be used to reduce BMD loss in the lumbar spine after allo-SCT, although it does not effectively prevent bone loss in the total hip or femoral neck. This is similar to other bisphosphonates used at recommended osteoporosis treatment dosage tested. Glucocorticoid therapy and tacrolimus therapy increased the risk of bone loss in the lumbar spine in patients following allo-SCT, and ibandronate appeared to mitigate these effects. Thus, ibandronate may be a good prophylactic treatment for patients exposed to high doses of glucocorticoids or prolonged use of tacrolimus. Results of our study are generalizable to patients following an allo-SCT especially those exposed to prolonged durations of immunosuppressive agents. It is noteworthy to mention that in prior studies there has been some evidence to suggest that ibandronate has a safer renal profile (GFR $> 30\,ml\,min^{-1}$) compared with other i.v. bisphosphonates such as zoledronic acid.[24,26–29] Thus, ibandronate may be a viable option in preventing bone loss especially in patients with pre-existing renal damage or those who develop renal insufficiency during the course of their allo-SCT. Furthermore, this trial evaluated doses used to treat post-menopausal osteoporosis and using higher doses in our patient population may need to be evaluated.

In clinical practice treatment compliance and tolerability are imperative in mitigating bone loss and fractures. Medications that are convenient to administer are preferred and ibandronate has these characteristics.[24] In addition, since all patients who have undergone allo-SCT experience bone loss, all patients should receive standard recommendations of calcium and vitamin D supplementation. Additional studies evaluating the effectiveness of pharmacological agents with different mechanisms of action to prevent and treat bone loss with the least amount of side effects are warranted.

Materials and Methods

Eligibility

We recruited patients for this study at The University of Texas MD Anderson Cancer Center from 1 January 2009 to 30 June 2010. Eligible patients were at least 18 years old and had undergone allo-SCT for the treatment of a hematologic malignancy or disorder within the previous 45 days. Patients with osteonecrosis of the jaw, and patients planning to have dental extractions were ineligible. Patients were also ineligible if they had pre-existing osteoporosis; a documented relapse; uncontrolled acute GVHD or uncontrolled infection; hypersensitivity to bisphosphonates; renal insufficiency; a recent history (within the

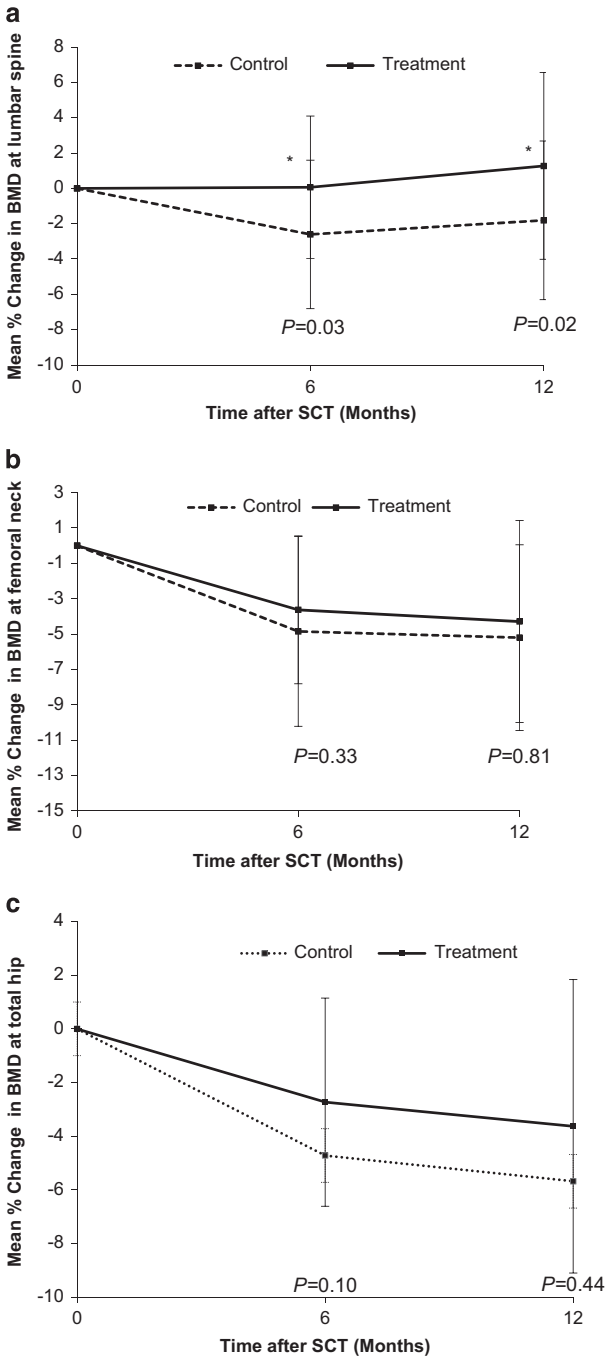


Figure 2 Mean percentage change in BMD between baseline and 6 months, and baseline and 12 months after allo-SCT at the lumbar spine (**a**), femoral neck (**b**) and total hip (**c**). *Denotes a significant difference between the treatment and control group.

previous 2 years) of bisphosphonate, calcitonin, anabolic steroid or daily oral fluoride supplement use; active bone lesions secondary to myeloma; hypocalcemia ($<8.4\,mg\,dl^{-1}$) or hypercalcemia ($>12.2\,mg\,dl^{-1}$ or $>10.3\,mg\,dl^{-1}$ with normal or elevated intact parathyroid hormone levels); 25-hydroxyvitamin D levels $<20\,ng\,ml^{-1}$ and evidence of osteomalacia; or a recent tooth extraction with evidence of infection or incomplete healing. This study was approved by the MD Anderson institutional review board. Written informed consent was obtained from all enrolled patients in accordance with institutional guidelines, and the study was designed in accordance with the Declaration of Helsinki II on the treatment of human subjects.

Protocol

This trial was designed as an open-label randomized trial to determine the effect of Ibandronate on reducing bone loss in patients following allo-SCT when compared with the control group. The design called for a total of 200 patients to be randomized with 1:1 ratio between the two arms. Patients were stratified based on their prior vitamin D supplementation usage (yes versus no) before randomization. For each stratum, a balanced randomization list was generated by the study statistician using RANLIST (https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware.aspx?Software_Id=29) with random balance points every 4 or 8 patients. This randomization list was provided to the research team and they kept it in a locked cabinet.

At each patient's enrollment the research nurse recorded demographic and relevant clinical characteristics, including history of GVHD and treatment with glucocorticoids and/or tacrolimus. The study coordinator randomly assigned all enrolled patients to the treatment or control group per the randomization list and the patient's stratification factor level. Patients who had vitamin D (25-hydroxyvitamin D) levels $>20\,ng\,ml^{-1}$ during their pre-transplant workup were treated with ergocalciferol (50 000 IU vitamin D_2) weekly for 12 weeks as part of standard care. This subset of patients were randomized separately into the treatment and control groups to ensure that each group had equal numbers of patients with corrected vitamin D deficiency.

Patients in the treatment group received one 3-mg dose of ibandronate intravenously over 15–30 s at entry, 3, 6 and 9 months after allo-SCT, for a total of 4 doses, in addition to elemental calcium (500 mg) and vitamin D 800 IU per day for the 12-month study period. Patients in the control group received the same regimen of calcium and vitamin D but not ibandronate. Patients who could not tolerate the calcium or vitamin D pills provided in the trial were allowed to use different brands of calcium or vitamin D with equivalent doses. Patients who were still taking the weekly ergocalciferol supplement had the option of not taking the twice-daily vitamin D supplements until they stopped taking the ergocalciferol.

We monitored serum calcium, magnesium, alkaline phosphatase, albumin and creatinine concentrations at baseline (up to 3 months prior to allo-SCT or prior to enrollment) and at 3, 6, 9 and 12 months (± 4 weeks) after allo-SCT. Levels of serum 25-hydroxyvitamin D, intact parathyroid hormone, and sex steroids (testosterone in men and estradiol in women) were checked at baseline and 12 months after allo-SCT.

Outcome measures

Patients were followed until 1 July 2011 for outcome assessment. The primary outcome measure was the percentage change in BMD in the lumbar spine, femoral neck and total hip at 6 and 12 months (± 4 weeks) after allo-SCT relative to baseline. We determined BMD by dual-energy x-ray absorptiometry (DEXA) for all patients at these time points at the Lumbar spine (L1–L4), femoral neck and total hip using Hologic QDR 1000 densitometer (Hologic, Waltham, MA, USA). The coefficients of variation of the DEXA scans of the lumbar spine, femoral neck and total hip were 1.06, 2.26 and 1.40%, respectively. Individual BMD values were expressed as $g\,cm^{-2}$ and *T*- and *Z*-scores. Quality control was performed by daily scanning of an anthropomorphic spine phantom.

Secondary outcome measures included the incidence of fractures, rates of stem cell engraftment and patient-reported adverse effects. Patient compliance with calcium and vitamin D was checked by recording the remaining pill count at every patient visit.

Statistical methods

Changes in BMD between baseline and 6 months and between baseline and 12 months were calculated as follows:

$$\frac{(BMD_{6\text{-month}} - BMD_{\text{baseline}})}{BMD_{\text{baseline}}} \times 100\% \quad \text{(Equation 1)}$$

$$\frac{(BMD_{12\text{-month}} - BMD_{\text{baseline}})}{BMD_{\text{baseline}}} \times 100\% \quad \text{(Equation 2)}$$

Continuous variables were summarized using mean, standard deviation and range; and were compared between the two treatment groups using Wilcoxon's rank-sum test. Categorical variables were summarized using frequency and percentage, and were compared between the two groups using Fisher's exact test.

The relationships between bone loss and cumulative glucocorticoid dose, cumulative tacrolimus dose, and acute and chronic GVHD were examined by linear regression analyses, with treatment (ibandronate versus control) as one of the covariates. Initially univariable linear regression models were fit for the BMD outcomes; variables with *P*-values $\leqslant 0.2$ were included in the final multivariable model. In the multivariable analysis, *P*-values $\leqslant 0.05$ were considered statistically significant. All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Assuming that the mean change in BMD at 12 months relative to baseline was a 12% decrease in the control group and a 0.1% decrease in the treatment group, a total of 120 patients (60 patients per group) would be needed to obtain 80% power to detect this difference at a two-sided significance level of 0.05, assuming a common s.d. of 0.23. Assuming a drop-out rate of 40% owing to mortality and relapse in the first year, a sample size of 200 patients would need to be enrolled into the study. The planned accrual period was 20 months, as we expected to enroll 10 patients per month on average.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

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References

1. Pundole XN, Barbo AG, Lin H, Champlin RE, Lu H. Increased incidence of fractures in recipients of hematopoietic stem-cell transplantation. *J Clin Oncol* 2015; **33**: 1364–1370.
2. Tauchmanova L, Colao A, Lombardi G, Rotoli B, Selleri C. Bone loss and its management in long-term survivors from allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2007; **92**: 4536–4545.
3. Yao S, McCarthy PL, Dunford LM, Roy DM, Brown K, Paplham P *et al.* High prevalence of early-onset osteopenia/osteoporosis after allogeneic stem cell transplantation and improvement after bisphosphonate therapy. *Bone Marrow Transplant* 2008; **41**: 393–398.
4. Yao S, Smiley SL, West K, Lamonica D, Battiwalla M, McCarthy Jr PL *et al.* Accelerated bone mineral density loss occurs with similar incidence and severity, but with different risk factors, after autologous versus allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2010; **16**: 1130–1137.
5. Ebeling PR, Thomas DM, Erbas B, Hopper JL, Szer J, Grigg AP. Mechanisms of bone loss following allogeneic and autologous hemopoietic stem cell transplantation. *J Bone Miner Res* 1999; **14**: 342–350.
6. Gandhi MK, Lekamwasam S, Inman I, Kaptoge S, Sizer L, Love S *et al.* Significant and persistent loss of bone mineral density in the femoral neck after haematopoietic stem cell transplantation: long-term follow-up of a prospective study. *Br J Haematol* 2003; **121**: 462–468.
7. Schulte C, Beelen DW, Schaefer UW, Mann K. Bone loss in long-term survivors after transplantation of hematopoietic stem cells: a prospective study. *Osteoporos Int* 2000; **11**: 344–353.
8. Weilbaecher KN. Mechanisms of osteoporosis after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2000; **6**: 165–174.
9. Stern JM, Sullivan KM, Ott SM, Seidel K, Fink JC, Longton G *et al.* Bone density loss after allogeneic hematopoietic stem cell transplantation: a prospective study. *Biol Blood Marrow Transplant* 2001; **7**: 257–264.
10. Giannini S, D'Angelo A, Carraro G, Nobile M, Rigotti P, Bonfante L *et al.* Alendronate prevents further bone loss in renal transplant recipients. *J Bone Miner Res* 2001; **16**: 2111–2117.
11. Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M *et al.* Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001; **12**: 1530–1537.
12. Shane E, Addesso V, Namerow PB, McMahon DJ, Lo SH, Staron RB *et al.* Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. *N Engl J Med* 2004; **350**: 767–776.
13. Shane E, Rodino MA, McMahon DJ, Addesso V, Staron RB, Seibel MJ *et al.* Prevention of bone loss after heart transplantation with antiresorptive therapy: a pilot study. *J Heart Lung Transplant* 1998; **17**: 1089–1096.
14. Tauchmanova L, Selleri C, Esposito M, Di Somma C, Orio Jr F, Bifulco G *et al.* Beneficial treatment with risedronate in long-term survivors after allogeneic stem cell transplantation for hematological malignancies. *Osteoporos Int* 2003; **14**: 1013–1019.
15. Tauchmanova L, De Simone G, Musella T, Orio F, Ricci P, Nappi C *et al.* Effects of various antireabsorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **37**: 81–88.
16. Hari P, DeFor TE, Vesole DH, Bredeson CN, Burns LJ. Intermittent zoledronic acid prevents bone loss in adults after allogeneic hematopoietic cell transplantation. *Biolo Blood Marrow Transplant* 2013; **19**: 1361–1367.
17. Kananen K, Volin L, Laitinen K, Alfthan H, Ruutu T, Valimaki MJ. Prevention of bone loss after allogeneic stem cell transplantation by calcium, vitamin D, and sex hormone replacement with or without pamidronate. *J Clin Endocrinol Metab* 2005; **90**: 3877–3885.
18. Grigg AP, Shuttleworth P, Reynolds J, Schwarer AP, Szer J, Bradstock K *et al.* Pamidronate reduces bone loss after allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2006; **91**: 3835–3843.
19. Tauchmanova L, Ricci P, Serio B, Lombardi G, Colao A, Rotoli B *et al.* Short-term zoledronic acid treatment increases bone mineral density and marrow clonogenic fibroblast progenitors after allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2005; **90**: 627–634.
20. Chae YS, Kim JG, Moon JH, Kim SN, Lee SJ, Kim YJ *et al.* Pilot study on the use of zoledronic acid to prevent bone loss in allo-SCT recipients. *Bone Marrow Transplant* 2009; **44**: 35–41.
21. Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST *et al.* Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. *Curr Med Res Opin* 2005; **21**: 391–401.
22. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A *et al.* Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004; **19**: 1241–1249.
23. Pyon EY. Once-monthly ibandronate for postmenopausal osteoporosis: review of a new dosing regimen. *Clin Ther* 2006; **28**: 475–490.
24. Rossini M, Orsolini G, Adami S, Kunnathully V, Gatti D. Osteoporosis treatment: why ibandronic acid? *Expert Opin Pharmacother* 2013; **14**: 1371–1381.
25. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; **83**: 1032–1045.
26. Body JJ. Bisphosphonates in metastatic bone disease: renal safety matters. *Oncologist* 2005; **10**(Suppl 1): 1–2.
27. Jackson GH. Renal safety of ibandronate. *Oncologist* 2005; **10**(Suppl 1): 14–18.
28. Munier A, Gras V, Andrejak M, Bernard N, Jean-Pastor MJ, Gautier S *et al.* Zoledronic Acid and renal toxicity: data from French adverse effect reporting database. *Ann Pharmacother* 2005; **39**: 1194–1197.
29. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. *Kidney Int* 2008; **74**: 1385–1393.

Supplementary Information accompanies the paper on the BoneKEy website (http://www.nature.com/bonekey).